Modeling Williams syndrome with induced pluripotent stem cells.

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Public Summary:
In this review, we provide a critical discussion on how the reprogramming technology allowed us to re-create mini-brains in a dish. The tool is helpful to dissect the molecular and cellular mechanisms responsible for the social brain, implicated in Williams Syndrome and autism.

Scientific Abstract:
The development of induced pluripotent stem cells (iPSCs) like never before has opened novel opportunity to study diseases in relevant cell types. In our recent study, Williams syndrome (WS), a rare genetic neurodevelopmental disorder, that is caused by hemizygous deletion of 25-28 genes on chromosome 7, is of interest because of its unique cognitive and social profiles. Little is known about haploinsufficiency effect of those deleted genes on molecular and cellular phenotypes at the neural level due to the lack of relevant human cellular model. Using the cellular reprogramming approach, we reported that WS iPSC-derived neural progenitor cells (NPCs) has increased apoptosis and therefore increased doubling time, which could be rescued by complementation of frizzled 9, one of the genes typically deleted in WS. Moreover, WS iPSC-derived CTIP2-positive pyramidal neurons exhibit morphologic alterations including longer total dendrites and increasing dendritic spine number. In addition, WS iPSC-derived neurons show an increase in calcium transient frequency and synchronized activity likely due to increased number of dendritic spines and synapses. Our work integrated cross-level data from genetics to behavior of WS individuals and revealed altered cellular phenotypes in WS human NPCs and neurons that could be validated in other model systems such as magnetic resonance imaging (MRI) in live subjects and postmortem brain tissues.